Non-Small Cell Lung Carcinoma in Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Case Report and Imaging Findings

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ABSTRACT

Background: Syndrome of inappropriate antidiuretic hormone secretion occurs due to unsuppressed anti-diuretic hormone secretion, leading to hyponatraemia and hypovolaemia or euvolemia. Etiologies range from drugs, central nervous system insults to malignancy. NSCLC accounts for 80-85% of lung cancers, however is only found in 2-4% of cases with SIADH.

Case summary: A 63 year old female presented with two week history of worsening constipation, urinary retention and lower back pain. Laboratory testing identified hyponatraemia, hyposmolality and CXR and CT chest revealed left lower zone mass. Biopsy confirmed NSCLC.

Conclusion: SIADH has a broad aetiology and may be due to rare pathologies such as NSCLC. A high index of suspicion should remain, as not all cases may present with respiratory symptoms and rare but critical diagnoses should not be missed.

CASE REPORT

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Patient information

A 63-year-old female presented to the emergency department with a two week history of worsening constipation, lower back pain and urinary retention. She had past medical history of anxiety disorder and previous lumbar spine metastases from squamous cell tongue cancer, for which she received radio and chemotherapy. She was an ex-smoker and denied any other environmental exposures. Home medications included telmisartan 80mg oral mane, citalopram oral 20mg mane, alprazolam 0.25mg twice a day as required for anxiety. Physical examination revealed unremarkable vital signs, frail appearance, euvolemic fluid status and reduced breath sounds in the left lower zone. The cardiac and neurological exam was normal. Laboratory results demonstrated hyponatraemia with low sodium of 116mmol/L (reference range 135 – 145 mmol/L), low serum osmolality of 154mmol/kg (reference range 275 – 295 mmol/kg) and urine osmolality was 189mmol/kg (elevated). Random urine sodium was 14 mmol/L (elevated). The suspicion was syndrome of inappropriate antidiuretic hormone release (SIADH). There were no causative drugs identified, no history of polydipsia, no central nervous system insults, no history of human immunodeficiency virus and no features of hereditary SIADH. Lumbar spine MRI ruled out cauda equina syndrome, A chest x-ray (CXR) was performed with suspicion for malignancy.

Imaging findings

CXR demonstrated a rounded soft tissue mass in the left lower lobe on anterio-posterior view, measuring 47mm in diameter. The remaining lungs had emphysematous changes. Cardiac size was within normal limits (Figure 1). Computer tomography (CT) of the chest with contrast demonstrated a solitary 34x25x24mm lobulated heterogenous enhancing, low attenuated lesion in the left lower lobe with irregular margins, highly concerning for malignancy (Figures 2a, 2b).

Histological Findings

A CT-guided lung biopsy was performed, and histological diagnosis of non-small cell lung carcinoma (NSCLC) was found. Haematoxylin and eosin staining demonstrates morphology of malignant neoplasm with irregular cell nests and extensive necrosis (Figure 3a). Tumour cells are positive for MNF116. There is focal staining of CK7 and CK5/6 also (Figure 3b). There is also Thyroid Transcription factor 1 (TTF1) positive nuclear staining (suggestive of lung adenocarcinoma and squamous cell carcinoma) and p40 positive staining (suggestive of squamous cell carcinoma of any site) (Figure 3c).

Management

A CT-guided lung biopsy was performed, and histological diagnosis of non-small cell lung carcinoma (NSCLC) was found. The patient was reviewed by medical oncology services and was unfit for chemotherapy or radiotherapy. The patient underwent palliative care.

Follow up

At three month follow up, the patient was deceased.

DISCUSSION

Etiology & Demographics

Lung cancer is the leading cause of cancer related death world-wide, with nearly two million deaths globally in 2020 [1]. The incidence is approximately 234,580 per year. 80% to 85% are NSCLC and 15-20% are small cell lung carcinoma. NSCLC has a higher incidence in males (56.4 new cases per 100,00) than females (45.3 new cases per 100,000) [2]. Etiologies include tobacco use (most common), alcohol use, asbestos exposure, radon, arsenic, chromium and nickel exposure as well as ionising radiation and polycyclic aromatic hydrocarbons exposure [3].

Clinical & Imaging Findings

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) occurs due to unsuppressed anti-diuretic hormone secretion, from either the pituitary gland or an extra-pituitary source. The syndrome is characterised by decreased water excretion, leading to hyponatraemia and hypo or euvolemia [4]. The Schwartz and Bartter criteria for diagnosis of SIADH are hyponatraemia (<135 mEq/L), decreased serum osmolality (<275 mOsm/kg), increased urine osmolality (>100 mOsm/kg), euvolemia, absence of other causes of hyponaetraemia (eg drugs, adrenal insufficiency) and correction of hyponatraemia by fluid restriction. Clinical features vary and include: nausea, malaise, headache, vomiting, lethargy, gait disturbance. Severe hyponatraemia may lead to seizures and coma. Etiologies include CNS disturbances (eg. stroke, infection), malignancies (commonly small cell lung carcinoma), drugs (eg. carbamezapine, sodium valproate), surgery, pulmonary disease, human immunodeficiency virus infection and hereditary SIADH [4].

NSCLC may present with cough, haemoptysis, chest pain or hoarseness. Bony metastases may present with fractures and pain. Brain metastases may present with confusion, headache, vomiting and visual field deficits [3]. Diagnosis of NSCLC as a cause SIADH is exceedingly rare with an incidence of only 2-4%. The pathogenesis of ADH secretion in NSCLC is not yet identified. One theory proposes ectopic arginine vasopressin (AVP), however a third of lung cancer patients do not demonstrate ectopic AVP release [5].

CXR findings of NSCLC include: a new or growing focal lesion, broadened mediastinum (concerning for lymph node involvement), atelectasis, pleural effusion or consolidation. CT-chest findings include: solitary pulmonary nodule, irregular or spiculated edges of the nodule, location in upper lobes and growth on serial imaging. Invasion may be assessed with contrast enhanced imaging [6].

Treatment & Prognosis

SIADH is managed by sodium correction and fluid restriction and vasopressin receptor antagonists in chronic refractory cases [4]. Treatment of NSCLC varies based on patient functional status and extent of spread. Stage I to III are treated with curative intent via surgery (lobectomy), radiation therapy or a combination. Stage IV is treated with systemic chemotherapy. Systemic therapy is targeted to specific gene mutations found via histological staining. For example, in a tumour that is epidermal growth factor receptor positive, a tyrosine kinase inhibitor such as osimertinib may be used [3].

Prognosis depends on stage and functional status of the patient. Overall, five-year survival is approximately 26.5% and as low as 10% in stage IV [7]. Poor prognostic factors include: poor functional status, pre-treatment weight loss, male sex and age [8].

Differential Diagnosis

The differential diagnoses of SIADH include all causes of hyponatraemia. They can be categorised by fluid volume status: euvolemic, hypovolaemic and hypervolemic. Causes include drugs, renal impairment, hormone impairment and surgery among others. SIADH falls under euvolemic hyponatremia [4]. Some differential diagnoses of NSCLC based on CXR and CT-Chest include: fibrosing mediastinitis, pulmonary tuberculosis or venous varices (table 1) [9].

ACKNOWLEDGEMENTS

Histology slides (Figure 3a, 3b and 3c) are provided by Dr. Lakshmy Nandakumar.

TEACHING POINT

SIADH has a broad aetiology and may be due to rare pathologies such as NSCLC. A high index of suspicion should remain, as not all cases may present with respiratory symptoms and a rare but critical diagnoses should not be missed.

QUESTIONS

Question 1: The overall leading cause of cancer deaths word wide is due to:

Answer 1 (applies): Lung cancer [Lung cancer is the leading cause of cancer related death world-wide, with nearly two million deaths globally in 2020 [1]

Answer 2: Prostate cancer

Answer 3: Colorectal cancer

Answer 4: Brain cancer

Answer 5: Renal cancer

Question 2: What proportion of lung canceers are NSCLC?

Answer 1 (applies): 80 – 85% (Lung cancer is the leading cause of cancer related death world-wide, with nearly two million deaths globally in 2020 [1]. The incidence is approximately 234,580 per year. 80% to 85% are NSCLC and 15-20% are small cell lung carcinoma.)

Answer 2: 20 - 30%
Answer 3: 30 - 40%
Answer 4: 40-50%
Answer 5: 50-60%

Question 3: The criteria for diagnosis of SIADH include:

Answer 1 (Applies): hyponatremia and decreased serum osmolality (The Schwartz and Bartter criteria for diagnosis of SIADH are: hyponatraemia (<135 mEq/L), decreased serum osmolality (<275 mOsm/kg), increased urine osmolality (>100 mOsm/kg), euvolemia, absence of other causes of hyponaetraemia (eg drugs, adrenal insufficiency) and correction of hyponatraemia by fluid restriction)

Answer 2: hypernatremia and decreased serum osmolality
Answer 3: hypernatremia and elevated serum osmolality
Answer 4: hypothyroidism and hypercortisolism
Answer 5: None of the above

Question 4: the overall five year survival for NSCLC is:

Answer 1: 26.5% (Overall, five-year survival is approximately 26.5% and as low as 10% in stage IV [7])

Answer 2: 80%
Answer 3: 90%
Answer 4: 100%
Answer 5: 2.65%

Question 5: The most common etiology of NSCLC is:

Answer 1 (applies): Tobacco use (Etiologies include tobacco use (most common), alcohol use, asbestos exposure, radon, arsenic, chromium and nickel exposure as well as ionising radiation and polycyclic aromatic hydrocarbons exposure [3])

Answer 2: Chromium exposure
Answer 3: Radon exposure
Answer 4: Asbestos exposure
Answer 5: Polycyclic aromatic hydrocarbons exposure

CONSENT

Patient had been consented (before passing away), prior to submitting of this manuscript

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FIGURES

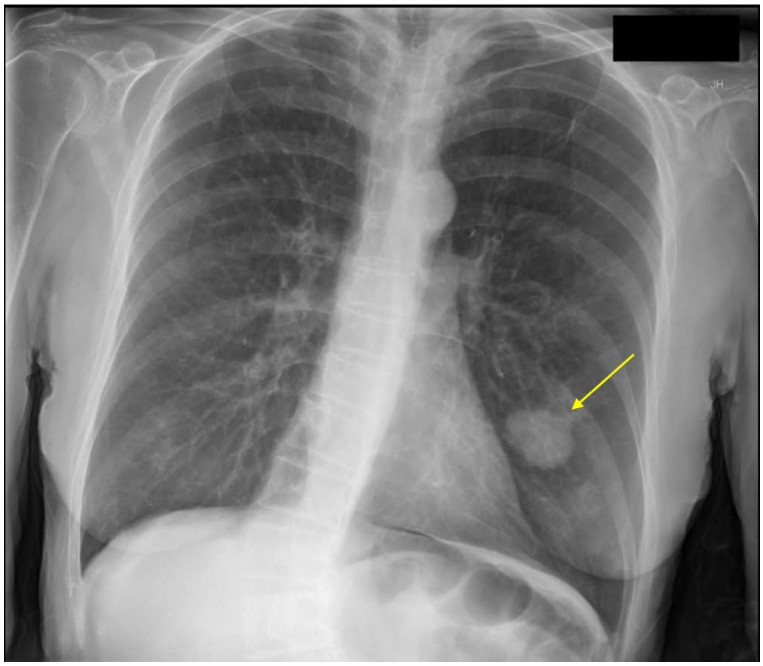

Figure 1: 63 year old female with CXR showing non-small cell lung carcinoma. Findings: anterio-posterior chest x-ray showing rounded soft tissue mass in the left lower lobe on anterio-posterior view, measuring 47mm in diameter

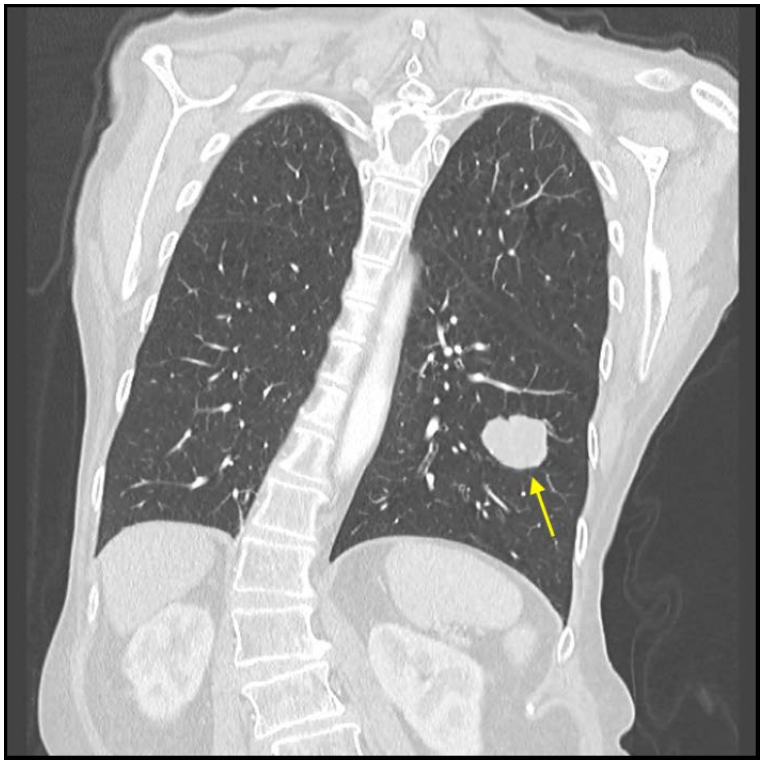

Figure 2a: 63 year old female with CT chest showing non-small cell lung carcinoma (arrow). Findings: Coronal contrast enhanced CT chest with a solitary 34x25x24mm lobulated heterogenous enhancing, low attenuated lesion in the left lower lobe with irregular margins. Technique: 100.00 kVP, 119mA, 3mm slices.

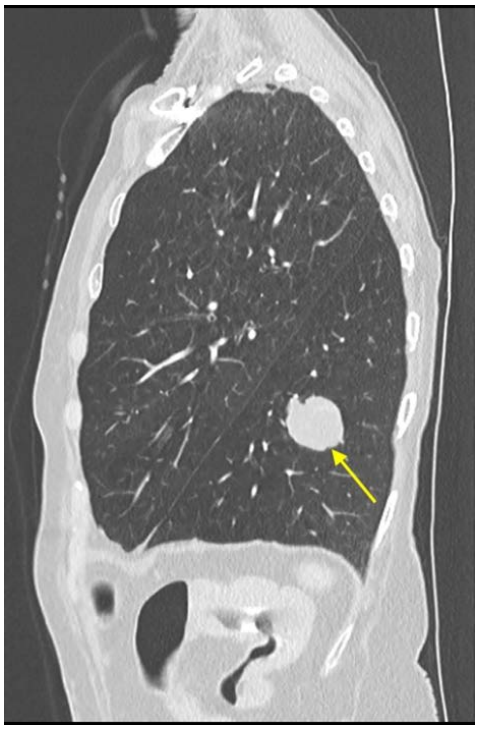

Figure 2b: 63 year old female with CT chest showing non-small cell lung carcinoma. Findings: Saggital contrast enhanced CT chest with a solitary 34x25x24mm lobulated heterogenous enhancing, low attenuated lesion in the left lower lobe with irregular margins. Technique: 100.00 kVP, 119mA, 3mm slices.

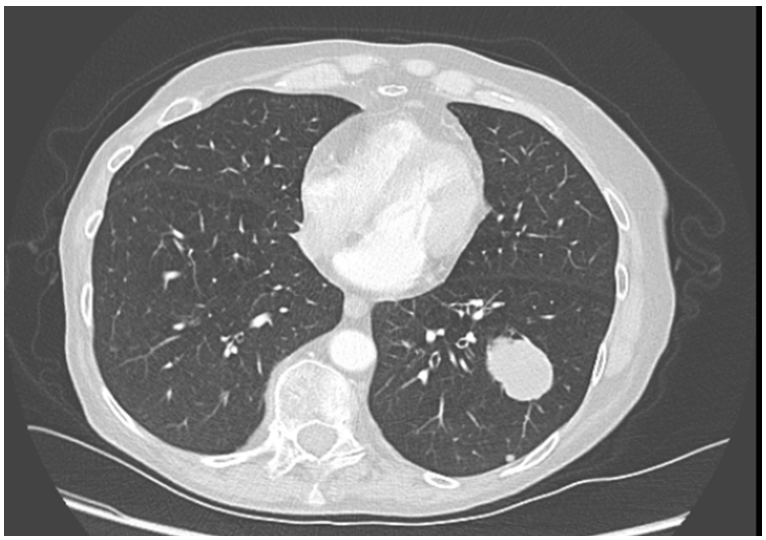

Figure 2c: 63 year old female with CT chest showing non-small cell lung carcinoma. Findings: Transverse, contrast enhanced CT chest with a solitary 34x25x24mm lobulated heterogenous enhancing, low attenuated lesion in the left lower lobe with irregular margins. Technique: 100.00 kVP, 119mA, 3mm slices.

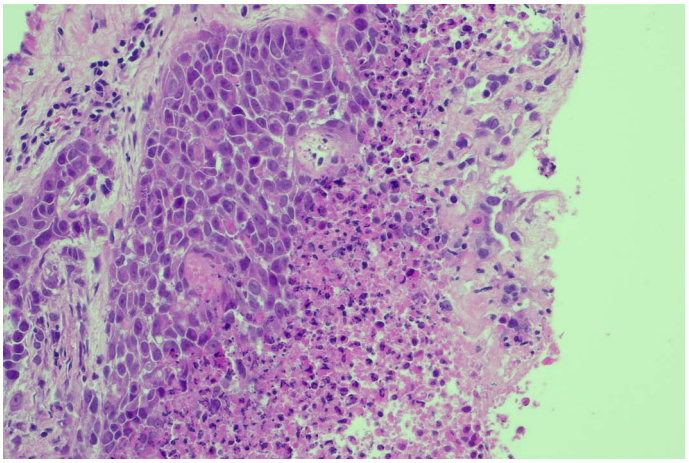

Figure 3a: 63 year old female with microscopic histopathology (20x magnification) showing non-small cell lung carcinoma: malignant neoplasm with irregular cell nests and extensive necrosis.

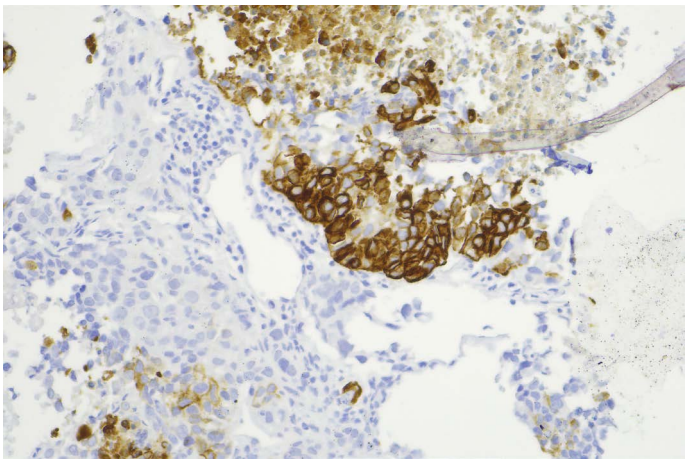

Figure 3b: 63 year old female with microscopic histopathology (20x magnification) showing non-small cell lung carcinoma: tumour cells are positive for MNF116. There is focal staining of CK7 and CK5/6.

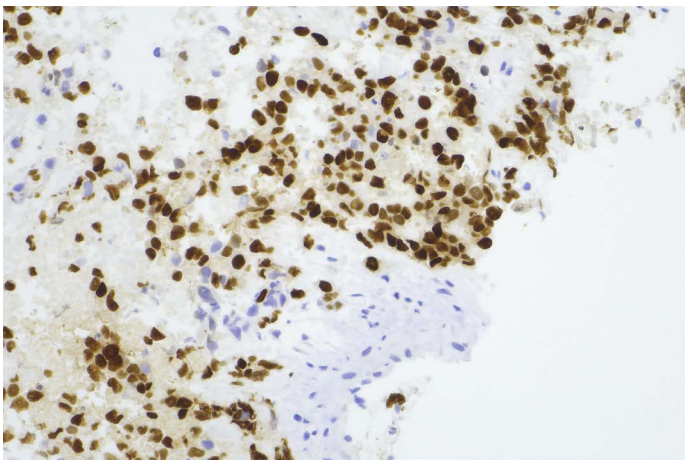

Figure 3c: 63 year old female with microscopic histopathology (20x magnification) showing non-small cell lung carcinoma: there is also Thyroid Transcription factor 1 (TTF1) positive nuclear staining (suggestive of lung adenocarcinoma and squamous cell carcinoma) and p40 positive staining (suggestive of squamous cell carcinoma of any site)

Table 1: NSCLC and Lung Cancer summary of key information [2,3,5]:

Aetiology and risk factors	Smoking, exposure to second hand smoke, asbestos, radon, arsenic, chromium, nickel, polycyclic aromatic hydrocarbons exposures, pulmonary fibrosis and human immunodeficiency virus.
Incidence of Lung Cancer	Approximately 234,580 per year.
Gender Ratio	higher incidence in males (56.4 new cases per 100,00) than females (45.3 new cases per 100,000)
Age Predilection	Nil
Treatment	Radiotherapy, Chemotherapy, Systemic therapy, Surgical resection.
Prognosis	Depends on stage and functional status of patient. Overall five year survival is 26.5%.
Imaging Findings on CXR	a new or growing focal lesion, broadened mediastinum (concerning for lymph node involvement), atelectasis, pleural effusion or consolidation.
Imaging findings on CT-Chest	solitary pulmonary nodule, irregular or spiculated edges of the nodule, location in upper lobes and growth on serial imaging.

DIFFERENTIAL TABLE

Table 2: Differential diagnoses [9]

	CXR	CT Chest
Non small cell lung carcinoma	new or growing focal lesion, broadened mediastinum (concerning for lymph node involvement), atelectasis, pleural effusion or consolidation.	solitary pulmonary nodule, irregular or spiculated edges of the nodule, location in upper lobes and growth on serial imaging
Fibrosing Mediastinitis	Non-specific widening of mediastinum, hilar calcification	Typically affects middle mediastinum with mass, calcifications
Tuberculoma	Well rounded mass typically in upper lobes, often solitary, up to 4cm	Regular, smooth outline, cavitation in the nodule, low attenuation
Venous Varices	Non specific mass	Pulmonary angiography delineating abnormal venous anatomy

KEYWORDS

Non-small cell lung cancer; syndrome of inappropriate antidiuretic hormone; chest; X-ray; computed tomography

ABBREVIATIONS

NSCLC = Non-Small Cell Lung Carcinoma
SIADH = Syndrome of Inappropriate antidiuretic hormone ADH release
CXR = Chest X-ray
CT = Computer tomography